

Vascular Normalization to Improve Treatment of COVID-19: Lessons from Treatment of Cancer

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ABSTRACT

The dramatic impact of the COVID-19 pandemic has resulted in an “all hands on deck” approach to find new therapies to improve outcomes in this disease. In addition to causing significant respiratory pathology, infection with SARS-CoV-2 (like infection with other respiratory viruses) directly or indirectly results in abnormal vasculature, which may contribute to hypoxemia. These vascular effects cause significant morbidity and may contribute to mortality from the disease. Given that abnormal vasculature and poor oxygenation are also hallmarks of solid tumors, lessons from the treatment of cancer may help identify drugs that can be repurposed to treat COVID-19. Although the mechanisms that result in vascular abnormalities in COVID-19 are not fully understood, it is possible that there is dysregulation of many of the same

angiogenic and thrombotic pathways as seen in patients with cancer. Many anticancer therapeutics, including androgen deprivation therapy (ADT) and immune checkpoint blockers (ICB), result in vascular normalization in addition to their direct effects on tumor cells. Therefore, these therapies, which have been extensively explored in clinical trials of patients with cancer, may have beneficial effects on the vasculature of patients with COVID-19. Furthermore, these drugs may have additional effects on the disease course, as some ADTs may impact viral entry, and ICBs may accelerate T-cell-mediated viral clearance. These insights from the treatment of cancer may be leveraged to abrogate the vascular pathologies found in COVID-19 and other forms of hypoxic respiratory failure.

The COVID-19 pandemic has transformed our world, causing staggering levels of morbidity and mortality globally. Although vaccines have been developed at record pace and immunosuppressive drugs have shown benefit in patient subgroups, improving the treatment of COVID-19 will remain an important goal until population immunity is achieved. Moreover, the yearly return of seasonal influenza suggests that even widespread vaccination will not completely eliminate COVID-19. At first glance, clinical oncology has little relevance in the treatment of COVID-19. However, as we learn more about the disease, it is possible that lessons from tumor biology will offer insights into improving therapies for COVID-19.

Like SARS-CoV, SARS-CoV-2 interacts with cells using the angiotensin converting enzyme 2 (ACE2) receptor and the transmembrane serine protease 2 (TMPRSS2; refs. 1–3). Unlike SARS-CoV, the SARS-CoV-2 spike protein has a furin cleavage site which may expand its tissue tropism via the use of additional receptors, such as neuropilin-1 (NRP1). NRP1 is a cell surface protein that serves as a coreceptor for VEGF (4–6). VEGF, an angiogenic growth factor that induces vascular leakage, is elevated in patients with COVID-19 (7). The VEGF-NRP1 pathway is involved in nociception, and there is evidence that the

SARS-CoV-2 spike protein can interfere with this pathway to block pain and other neuronal signals (5, 8). It is not known, however, whether SARS-CoV-2 binding to NRP1 affects VEGF signaling through VEGFR2 in endothelial cells.

The ACE2, NRP1, and TMPRSS2 proteins are expressed on multiple cell types, including endothelial cells (9), and there is evidence that the virus can infect the endothelium, both in the lungs and throughout the body (10, 11). Even if SARS-CoV-2 infection is restricted to lung epithelium, the virus can have widespread effects on vasculature by causing a systemic inflammatory state (12–14). Whether through direct infection or systemic inflammation-induced endotheliitis, COVID-19 can result in vascular damage, loss of vascular integrity, and thrombosis. The direct effects of SARS-CoV-2 on the vasculature may be a mechanism of severe disease, independent of primary respiratory infection, epithelial damage, and impaired ventilation (15–17).

COVID-19–related vascular abnormalities have some resemblance to those seen in malignant solid tumors (11, 14, 18), and multiple nonmalignant diseases (e.g., macular degeneration, schwannomas, and tuberculosis; ref. 19). Blood vessels in tumors are structurally abnormal and often hyperpermeable, having large intercellular openings in the endothelial lining (Fig. 1). These vascular abnormalities are caused by the overexpression of proangiogenic factors and/or under-expression of antiangiogenic factors (20). The large openings in the tumor vessel wall can cause fluid leakage to the extravascular space, compromising blood perfusion and exacerbating tissue hypoxia (21). The resulting impaired perfusion and hypoxia are two major barriers to cancer treatment: the former compromises uniform delivery of drugs and immune cells, and the latter attenuates the killing potential of tumor reactive immune cells even after they accumulate in the tumor microenvironment.

COVID-19 exhibits a number of clinical features similar to those seen in patients with cancer, including increased tissue factor activation, presence of neutrophil extracellular traps, and activated platelets (22–26). Loss of integrity of both the epithelial and endothelial components of the alveolar-capillary membrane is a primary

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Translational Relevance

While vaccines are offering hope in preventing COVID-19, there remains an urgent need for rapidly deployable therapeutics for patients with established infections. Moreover, the COVID-19 pandemic has once again highlighted the lack of effective therapies for the most severe form of hypoxemic respiratory failure, the acute respiratory distress syndrome (ARDS). ARDS in general, and in COVID-19 in particular, is associated with vascular complications and life-threatening coagulopathy. We propose that some therapies currently being tested in clinical trials (androgen deprivation therapy and immunotherapies) will have the additional benefit of normalizing the vasculature and reducing thrombosis in patients with COVID-19. Thus, these drugs may have dual roles, both in modifying the course of disease, as well as preventing vascular complications of COVID-19. Combinations of these drugs, which have been extensively studied in the oncology space, could be repurposed to ameliorate the tremendous morbidity and mortality of COVID-19.

mechanism of impaired ventilation and hypoxemia in acute respiratory distress syndrome (ARDS) and COVID-19 (27). In addition, endothelial disruption and the resulting thrombosis may lead to impaired perfusion of normally ventilated lung and more extensive hypoxemia (28). Although the lung is exposed to higher levels of ambient oxygen than tumors, alveolar pO_2 levels in the setting of V/Q mismatch are lower than normal, and relative alveolar hypoxia has been linked to inflammation (29). Alveolar hypoxia may also trigger abnormal angiogenesis, ultimately increasing inflammation by allowing inflammatory cells to accumulate in larger numbers. Endothelial dysfunction may be significantly worse in patients with diabetes, obesity, and renal dysfunction (30), all conditions associated with increased mortality from COVID-19 (31).

The fact that vascular abnormalities are common in COVID-19 raises the question of whether some therapies that can improve the function of the vasculature may help control the disease. There are important gender differences in COVID-19, with men having a higher risk of developing severe disease and death compared with women (32). Although there is no evidence of androgen excess in COVID-19, TMPRSS2, an androgen-responsive serine protease, is more abundant in males in some tissues (9, 33), potentially contributing to the observed increased risk for disease severity in men. The involvement of TMPRSS2 and furin in the activity of the virus has also led to the hypothesis that inhibition of these proteases might block virus infection and inhibit systemic dissemination (e.g., NCT04353284 and NCT04583592 are testing the TMPRSS2 inhibitor, camostat mesylate, in patients with COVID-19). In addition to direct inhibition of these proteases, multiple androgen deprivation therapies (ADT) are being tested in COVID-19 clinical trials, including the androgen receptor blockers, bicalutamide (NCT04509999 and NCT04374279) and proxalutamide (NCT04446429), and the GnRH antagonist, degarelix (NCT0439771).

Interestingly, androgen withdrawal also has beneficial effects on vasculature. We have shown that castration-induced androgen withdrawal in androgen-dependent tumors (e.g., prostate cancer) can potentiate vascular normalization by suppressing the effects of androgen-dependent expression of VEGF (34).

These indirect effects of androgen deprivation on vasculature are similar to those observed when VEGF is inhibited directly. We have

shown in preclinical and clinical studies that blockade of VEGF and/or other proangiogenic factors (e.g., angiopoietin-2) can transiently normalize vessels, fortifying the tumor vessel wall and reducing vascular permeability (20, 35). This, in turn, restores the functionality of the tumor vessels, increasing delivery of oxygen, drugs, and immune cells to the tumor tissue. Better vascular function improves treatment outcomes for not only multiple malignant diseases, but also for many nonmalignant diseases characterized by abnormal blood vessels (e.g., macular degeneration, schwannomas, and tuberculosis; ref. 19). Interestingly, angiopoietin-2 levels predict severity of ARDS (36), and targeting of angiopoietin-2 by mAbs improved survival in animal models of ARDS (37).

Therefore, based on lessons from cancer treatment, we propose that ADTs can have a dual benefit for patients with androgen-dependent cancers who are also infected by SARS-CoV-2, as it could enhance cancer therapy by normalizing tumor vessels, attenuate vascular leakage and, in the case of some ADT drugs such as camostat, interfere with virus propagation by reducing TMPRSS2-mediated viral entry. Together, these effects may help mitigate the severity of COVID-19. Retrospective analysis of men in the Veneto region of Italy showed that patients with prostate cancer receiving ADT had a significantly lower risk of SARS-Cov-2 infection compared with patients not receiving ADT (38), and a smaller cohort from New York showed lower rates of hospitalizations in an ADT prostate cancer cohort (39). However, this remains an open question as other cohorts have shown no effect (40). In patients with prostate cancer, the accumulating evidence regarding the potential ability of ADT to reduce SARS-CoV-2 infectivity should be considered in weighing the risks and benefits of starting or restarting ADT.

While the risks of ADT likely preclude its use in other contexts, our argument might be extended to patients with other, nonandrogen-dependent cancers by considering how SARS-CoV-2 affects the vasculature. If COVID-19 affects the vasculature directly through infection, as well as indirectly through a hyperinflammatory state, effective treatments should involve not only the inhibition of the virus activity, but also the stabilization of the vasculature throughout the body. Furthermore, with other coronaviruses, infection causes downregulation of the viral entry receptor, ACE2 (41), which can result in increased VEGF signaling in the context of acute lung injury (42). Thus, antagonizing VEGF, indirectly via ADT for androgen-dependent tumors or directly using anti-VEGF/R agents, could decrease blood vessel leakiness, mitigating some of the damage caused by the virus-induced inflammation and improving perfusion in the vessels. This could potentially decrease thrombosis and accumulation of inflammatory cells in the lung and reduce hypoxemia by increasing perfusion (43).

Although VEGF blockade has been associated with some thromboembolic complications (44), these can often be managed with anticoagulation (42, 45–49). The relationship between VEGF inhibition and coagulation may require careful dose titration to find the optimum balance of pro- and antithrombotic effects, similar to optimizing the dose and schedule of anti-VEGF agents for cancer treatment (50). Therefore, it is possible that inhibiting VEGF, either directly or indirectly, can improve cancer therapy in androgen-independent, as well as androgen-dependent tumors by normalizing the tumor vessels, with the additional benefit of limiting the severity of COVID-19. This concept is currently being tested in a number of clinical trials using antiangiogenic therapy in patients with COVID-19 (NCT04275414, NCT04344782, NCT04305106, and NCT04511650).

To further leverage our toolbox developed for cancer research, we recently repurposed a mathematical model for cancer to simulate

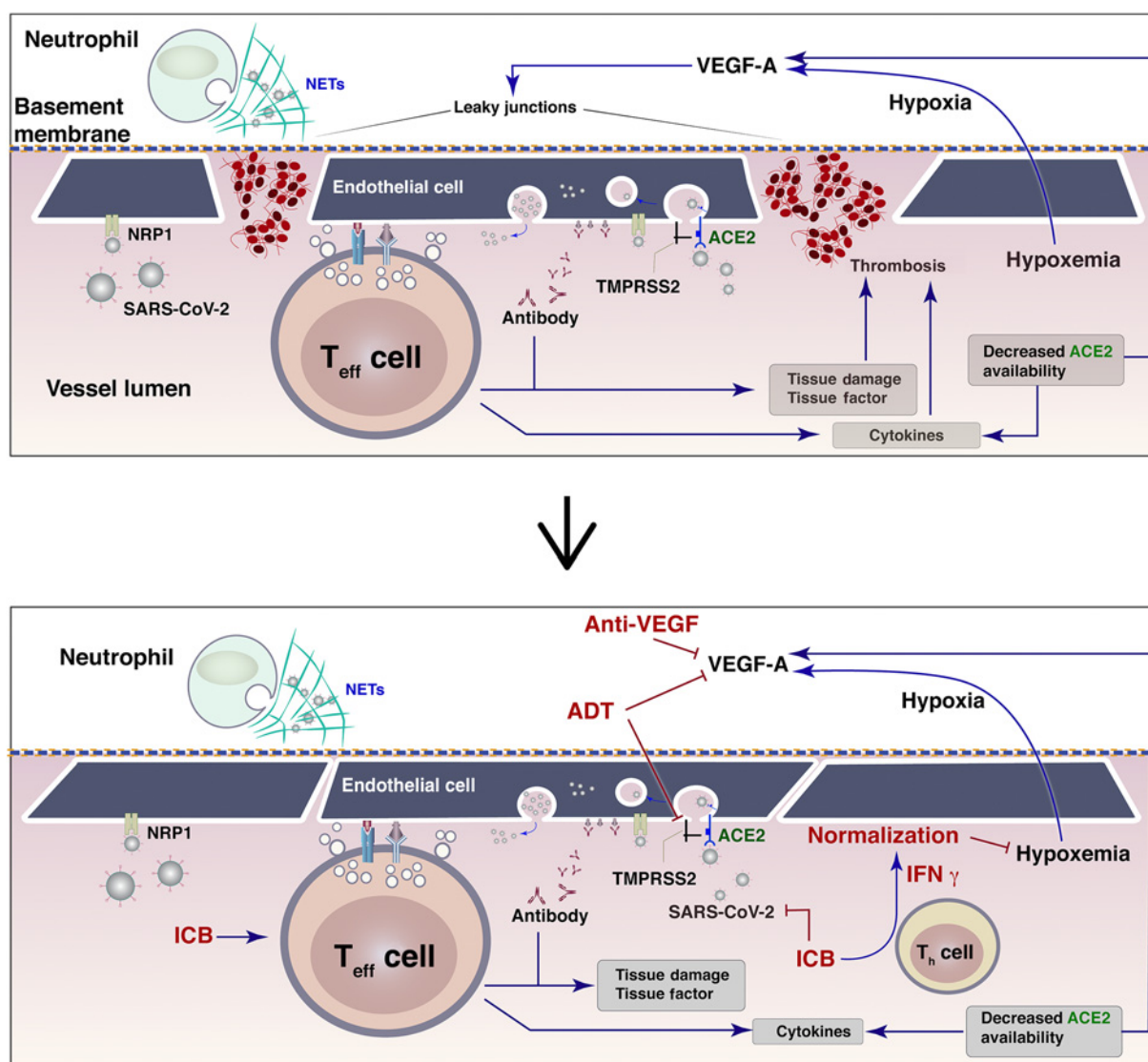


Figure 1.

Normalization of vasculature to limit thrombosis in COVID-19. Endothelial damage and vasculitis caused by viral infection, immune cell cytotoxic activity, and elevated cytokine levels can expose basement membrane and induce tissue factor and thrombosis. Sluggish blood flow, impaired ventilation, and hypoxemia can also upregulate VEGF-A, which further increases vessel leakiness and access of plasma proteins and platelets to the subendothelial matrix. We propose that ADT, in addition to affecting TMPRSS2-mediated viral entry into the cell, will help restore endothelial barrier function, thus limiting thrombosis. Furthermore, treatment with anti-VEGF drugs and/or immune checkpoint blockers in the early stage of the disease can normalize vessels and limit viral damage to the endothelium, allowing vascular repair and preventing thrombosis. NET, neutrophil extracellular trap; T_{eff} cell, effector T cell; T_h cell, helper T cell.

various COVID-19 treatment strategies. The model predicts that optimal clinical management of COVID-19 depends on the rapid response of activated effector $CD8^+$ T cells (51). In our model, early control of the virus by adaptive immunity prevents the out-of-control, self-fueling innate immune response that results in poor outcomes in some patients (51). On the basis of this finding, we propose that immune checkpoint blockers (ICB), which have revolutionized the treatment of many types of cancer, can also be employed to improve COVID-19 therapy. Indeed, it has been shown that TIM-3, a coinhibitory molecule present on T cells, is upregulated in the plasma of patients with COVID-19 (52). Furthermore, there has been interest in using ICBs in many chronic (e.g., human immunodeficiency virus and Hepatitis B and C) and acute viral diseases (e.g., influenza; ref. 53). Our

simulations predict that ICBs, when given early in the disease course, can act at multiple levels against COVID-19 progression. Specifically, activation of $CD8^+$ T cells can increase the killing of virus-infected cells, which, in turn, decreases the production of proinflammatory cytokines (e.g., IL6). This model suggests that having inflammation under control, in turn, can reduce the accumulation of macrophages, neutrophils, and other cells of the innate immune system and also inhibit coagulation and blood vessel thrombosis. ICBs are also predicted to cause indirect antiviral effects by increasing production of IFN, thus limiting viral replication.

Interestingly, recent studies show that the use of ICBs for cancer therapy not only activates $CD4^+$ and $CD8^+$ T cells to elicit antitumor responses, but can also indirectly normalize the tumor vasculature by

increasing the production of IFN γ , and thus improves tumor blood vessel functionality (54–56). Therefore, similar to ADT and direct anti-VEGF drugs, it is possible that ICBs could also normalize the SARS-CoV-2-infected vessels. The timing of ICBs for treating COVID-19 must be considered carefully, however, as it is now well established that patients with severe COVID-19 benefit from immunosuppression. If given too late, that is, after the innate immune system is already ramping up, and the virus is not controlled by adaptive immunity, ICBs could exacerbate the systemic inflammatory response and worsen disease outcomes. This scenario is particularly concerning, given that ICBs can cause life-threatening pneumonitis in a small number of patients (57). In fact, initial reports suggested that ICB use was associated with more severe COVID-19 disease (58), raising concerns about immune hyperactivation. However, data from larger cohorts have been more reassuring, suggesting that there may be a complex interplay between ICB and COVID-19 disease progression (59–63). These data raise the possibility that judicious use of ICBs may be considered in some patients with COVID-19, as has been proposed in several clinical trials (e.g., NCT04356508).

Of course, the risk–benefit analysis for ICBs is complicated by the possibility of immune-related adverse events, including myocarditis, which in some cases can be life threatening (64). Furthermore, ICBs can be associated with other rare significant immune-mediated complications (65, 66). These risks vary depending on the choice of PD-1/PD-L1 or CTLA-4 inhibitors and can be more severe with combined therapy. Given that the median time of onset of grade >3 immune-related adverse events is between 3 and 6 months (65, 66), there may be a window where a short course of ICB may be less likely to cause toxicity. Clearly, robust biomarkers for early identification of patients who are likely to develop severe disease would be essential to guide ICB therapy of patients with COVID-19.

ICBs could be combined with other therapeutics against COVID-19, such as antiviral, anti-inflammatory, and antithrombotic drugs. Indeed, the combination of antiangiogenic agents and ICBs has been shown to further improve vascular efficiency and treatment outcomes in preclinical models of cancer (67, 68), and the FDA has approved five such combinations in the past 2 years. Given the commonalities between the tumor vasculature and the blood vessels affected by SARS-CoV-2, leveraging the experience of vascular normalization in cancer may provide novel therapeutic strategies for COVID-19 (56, 69). Again, these approaches also

have the potential for significant side effects and toxicity and will need to be tested in carefully designed clinical trials.

Tools that can identify patients likely to develop severe COVID-19, or more specifically, endotypes of disease with prominent vasculopathy, would help identify patients that may benefit from vascular normalization and maximize the therapeutic ratio. These patients could then be enrolled on trials of already FDA-approved drugs in the ICB, ADT, and/or VEGF pathways. We anticipate that such a collaborative effort between multiple different disciplines may yield promising new treatments for this public health crisis by repurposing drugs already approved for various malignancies. Moreover, the knowledge gained from the study of COVID-19 coagulopathy may point to therapies for other forms of ARDS, an ongoing health crisis for which there exists almost no specific therapies.

Authors' Disclosures

L.L. Munn reports grants from NIH during the conduct of the study, personal fees from Bayer, other from SimBioSys outside the submitted work, owns equity in Bayer AG, and is consultant for SimBioSys. Neither any reagent nor any funding from these organizations was used in this study. N.K. Jain and R.K. Jain report honorarium from Amgen; consultant fees from Chugai, Elpis, Merck, Ophthotech, Pfizer, SPARC, SynDevRx, and XTuit; equity in Accurius, Enlight, Ophthotech, and SynDevRx; they are members of boards of trustees of Tekla Healthcare Investors, Tekla Life Sciences Investors, Tekla Healthcare Opportunities Fund, Tekla World, and Healthcare Fund; and a grant from Boehringer Ingelheim. R.K. Jain reports NIH funding for other research projects not related to this article and has also received fees and equity from companies as an advisor/board member not related to this work. No disclosures were reported by the other authors.

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